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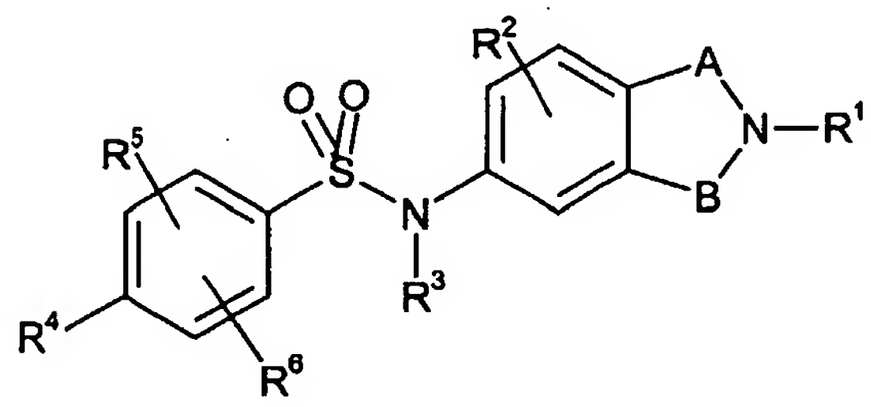
(54) Title: BENZENESULFONAMIDE DERIVATIVES



(I)

(57) Abstract: The invention provides compounds of formula (I) wherein A and B represent the groups $-(CH_2)m-$ and $-(CH_2)n-$ respectively; R^1 represents hydrogen or C_{1-6}alkyl; R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pC_{3-6}$cycloalkyloxy, $-COC_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-COC_{1-6}$alkyl, $-CO_2NR^7R^8$, $-SO_2NR^7R^8$, $-(CH_2)pNR^7R^8$, $-(CH_2)pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl or a fused bicyclic heterocyclic ring system; R^3 represents hydrogen or C_{1-6}alkyl; R^4 represents halogen, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl or $-(CH_2)_pC_{3-6}$cycloalkyloxy; R^5 and R^6 each independently represent hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pC_{3-6}$cycloalkyloxy, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^7R^8$, $-SO_2NR^7R^8$, $-(CH_2)_pNR^7R^8$, $-(CH_2)_pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl or a fused bicyclic heterocyclic ring system; R^7 and R^8 each independently represent hydrogen or C_{1-6}alkyl;m and n independently represent an integer selected from 1 and 2;p independently represents an integer selected from 0, 1, 2 and 3; or a pharmaceutically acceptable salt or solvate thereof,with the proviso that the compounds 4-methyl-N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-benzenesulfonamide, 7-(4-chlorophenyl)sulfonamido-1,2,3,4-tetrahydroisoquinoline hydrochloride and N-(2-ethyl-5-isoindolinyl)-p-toluenesulfonamide are excluded.The compounds are useful in therapy, in particular as antipsychotic agents.

WO 03/068732 A2

Benzenesulfonamide Derivatives

This invention relates to novel compounds, pharmaceutical compositions containing them and their use in therapy, in particular as antipsychotic agents.

EP266949 describes tetrahydroisoquinolin-2-yl derivatives of carboxylic acids as thromboxane A2 antagonists.

US4321254 describes antiallergic imidodisulfamides. 7-(4-Chlorophenylsulphonamido)-1,2,3,4-tetrahydroisoquinoline hydrochloride is disclosed as an intermediate in the preparation of imidodisulfamides.

WO96/35713 and WO96/38471 describe dipeptides which promote the release of growth hormone. 4-Methyl-(N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-benzenesulfonamide is disclosed as an intermediate in the preparation of these peptides in both of these applications.

N-(2-Ethyl-5-isoindolinyl)-p-toluenesulfonamide is cited in Beilstein (CAS Registry Number 3606-74-4) as being disclosed in patent DE36431. However, this citation is apparently erroneous, as no disclosure of this compound is made in DE36431.

WO 01/62737 discloses amino pyrazole derivatives useful for the treatment of obesity and other disorders associated with the NPY receptor subtype Y5.

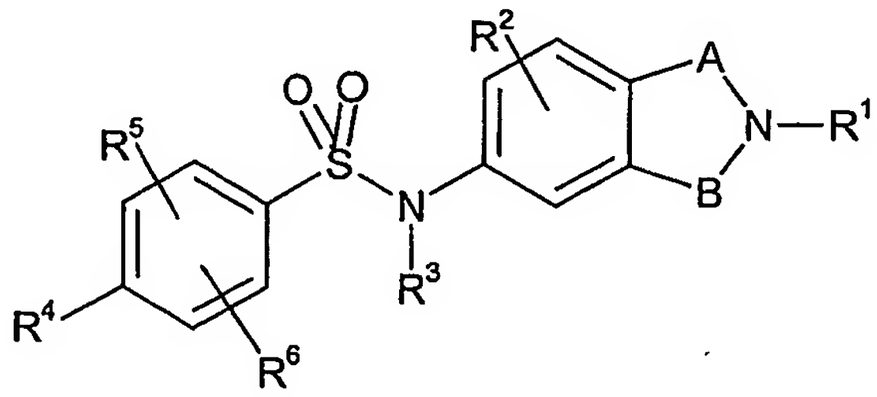
EP0937723 discloses sulfonamide compounds useful in the treatment of thrombolytic disorders.

WO 01/85695 discloses tetrahydroisoquinoline analogues useful as growth hormone secretagogues.

US 5,684,195 discloses a method of preparing sulfonamides from sulfones.

WO 02/46164 discloses aryl sulfonamide compounds that are said to be useful as selective ER-β ligands in the treatment or prophylaxis of Alzheimer's disease, anxiety disorders, depressive disorders, osteoporosis, cardiovascular disease, rheumatoid arthritis or prostate cancer.

According to the invention, there is provided a compound of formula (I):



(I)

wherein

A and B represent the groups $-(CH_2)_m-$ and $-(CH_2)_n-$ respectively;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pC_{3-6}$cycloalkyloxy, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^7R^8$, $-SO_2NR^7R^8$, $-(CH_2)_pNR^7R^8$, $-(CH_2)_pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl or a fused bicyclic heterocyclic ring system;

R^3 represents hydrogen or C_{1-6}alkyl;

R^4 represents halogen, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, -$(CH_2)_pC_{3-6}$cycloalkyl or -$(CH_2)_pC_{3-6}$cycloalkyloxy;

R^5 and R^6 each independently represent hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, -$(CH_2)_pC_{3-6}$cycloalkyl, -$(CH_2)_pC_{3-6}$cycloalkyloxy, -COC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SOC_{1-6}alkyl, -S-C_{1-6}alkyl, -CO_2C_{1-6}alkyl, -$CO_2NR^7R^8$, -$SO_2NR^7R^8$, -$(CH_2)_pNR^7R^8$, -$(CH_2)_pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl or a fused bicyclic heterocyclic ring system;

R^7 and R^8 each independently represent hydrogen or C_{1-6}alkyl;

m and n independently represent an integer selected from 1 and 2;

p independently represents an integer selected from 0, 1, 2 and 3;

or a pharmaceutically acceptable salt or solvate thereof,

with the proviso that the compounds 4-methyl-N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-benzenesulfonamide, 7-(4-chlorophenyl)sulfonamido-1,2,3,4-tetrahydroisoquinoline hydrochloride and N-(2-ethyl-5-isoindolinyl)-p-toluenesulfonamide are excluded.

As a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore, with the proviso that when R^1 and R^3 both represent hydrogen and A and B both represent $(CH_2)_2$, R^4 does not represent methyl or ethyl.

As a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore, with the proviso that when R^1, R^2 and R^3 all represent hydrogen and A and B both represent $(CH_2)_2$, R^4 does not represent methyl or ethyl.

As a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore, with the proviso that when A and B both represent $(CH_2)_2$, R^3 represents hydrogen and R^4 represents halogen, R^1 does not represent hydrogen.

As a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore, with the proviso that when A and B both represent $(CH_2)_2$, R^2 and R^3 both represent hydrogen and R^4 represents halogen, R^1 does not represent hydrogen.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl.

As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, n-butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C_{3-7}cycloalkyl means a non-aromatic

ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_{6-7}cycloalkyl group is preferred.

As used herein, the term "halogen" refers to the elements fluorine, chlorine, bromine and iodine.

As used herein, the term "aryl" refers to a phenyl ring or a naphthyl ring.

As used herein, the term "heteroaryl" refers to a 5- or 6-membered heterocyclic aromatic ring or a fused bicyclic heterocyclic ring system.

As used herein, the term "5- or 6-membered heterocyclic aromatic ring" refers to a monocyclic unsaturated ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Examples of suitable 5- and 6-membered heterocyclic aromatic rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, isothiazolyl and isoxazolyl.

As used herein, the term "fused bicyclic heterocyclic ring system" refers to a ring system comprising two 5- to 7-membered saturated or unsaturated rings, the ring system containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, each ring has 5 or 6 ring atoms. Examples of suitable fused bicyclic rings include, but are not limited to, indolyl, indolinyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzodioxanyl, indanyl and tetrahydronapthyl. Further examples include, but are not limited to, quinolizinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, isoindolyl, indolizinyl, indazolyl, pyrrolopyridinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, dihydrobenzothienyl, dihydrobenzofuranyl, benzodioxolanyl, methylenedioxyphenyl, dihydrobenzodioxinyl and the like.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Most preferably the solvent used is water and the solvate may also be referred to as a hydrate.

It will be appreciated that for use in medicine the salts of formula (I) should be physiologically acceptable. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other non-physiologically acceptable salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of the compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms thereof.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

The groups R^2, R^5 and R^6 may be located on any position on their respective phenyl rings.

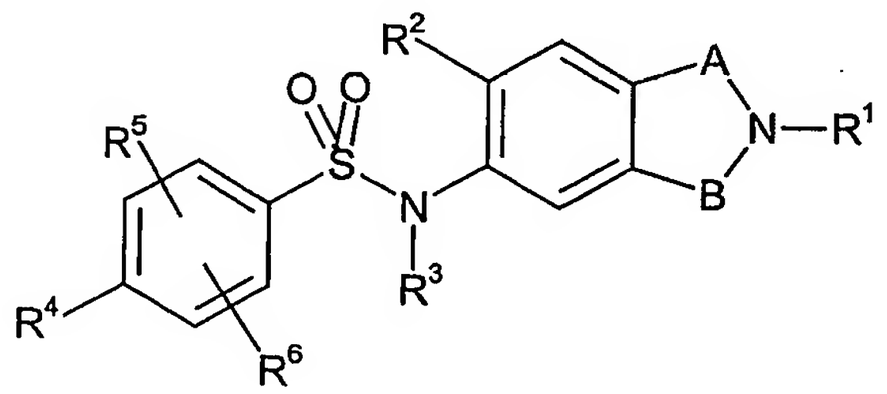
When R^2, R^5 or R^6 represent optionally substituted aryl or optionally substituted heteroaryl, the optional substituents may be independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano and –S-C_{1-6}alkyl.

Preferably, R^1 represents hydrogen or C_{1-4}alkyl. More preferably, R^1 represents hydrogen, methyl, ethyl, n-propyl or isopropyl. Even more preferably, R^1 represents hydrogen, methyl or isopropyl.

In a more preferred embodiment, the R^2 group is located at the para-position relative to the group B.

Preferably, R^2 represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy. More preferably, R^2 represents hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy. Even more preferably, R^2 represents hydrogen, bromine, ethyl, methoxy, ethoxy or isopropoxy. Even more preferably, R^2 represents hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy located at the para-position relative to the group B.

i.e. a compound of formula (IA)



(IA)

or a pharmaceutically acceptable salt or solvate thereof wherein groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore.

For compounds of the formula (I) or (IA), preferably, R^3 represents hydrogen or C_{1-4}alkyl. More preferably, R^3 represents hydrogen, methyl, ethyl, n-propyl or isopropyl. Even more preferably, R^3 represents hydrogen, methyl or isopropyl.

For compounds of the formula (I) or (IA), preferably, R^4 represents C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}cycloalkyl, halogen, trifluoromethyl or trifluoromethoxy. More preferably, R^4 represents C_{1-6}alkyl, C_{1-4}alkoxy, iodine, cyclohexyl, trifluoromethyl or trifluoromethoxy.

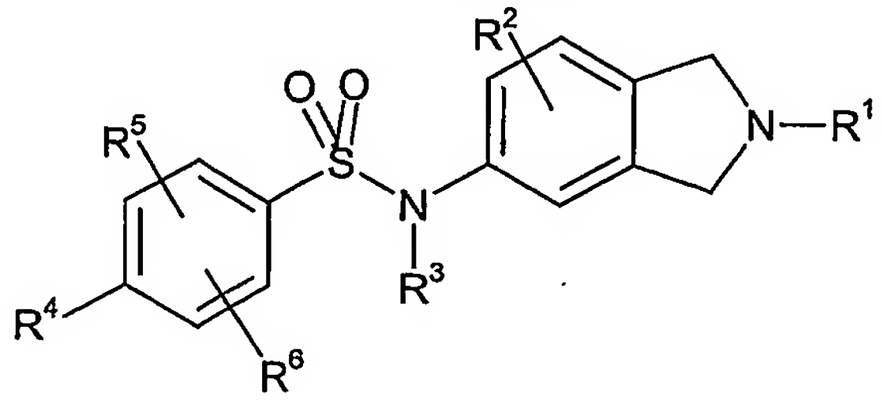
For compounds of the formula (I) or (IA), preferably, the optional substituents for the groups R^2, R^5 and R^6 are selected from chlorine, fluorine, bromine, methyl, ethyl, t-butyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano and –S-methyl.

For compounds of the formula (I) or (IA), preferably, R^5 and R^6 independently represent hydrogen.

For compounds of the formula (I) or (IA), preferably, R^7 and R^8 independently represent hydrogen or C_{1-4}alkyl. More preferably, R^7 and R^8 independently represent hydrogen or methyl.

For compounds of the formula (I) or (IA), preferably, p represents 0.

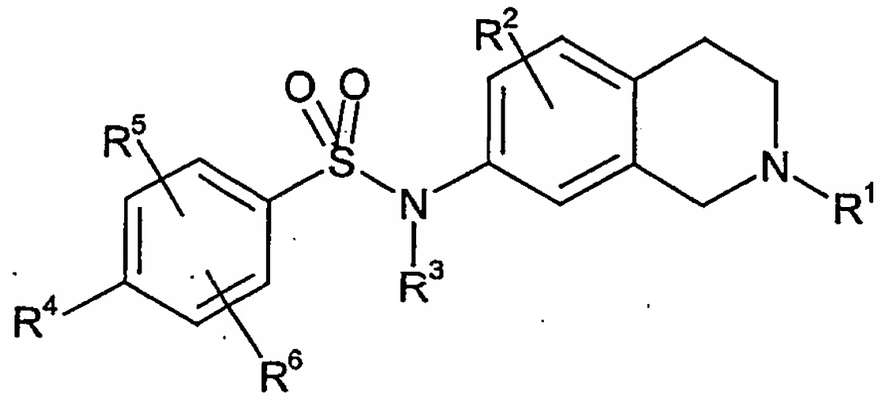
In a preferred aspect, m is 1 and n is 1 and the invention is a compound of formula (IB):



(IB)

or a pharmaceutically acceptable salt or solvate thereof wherein groups R^1 to R^6 have any of the meanings as given hereinbefore.

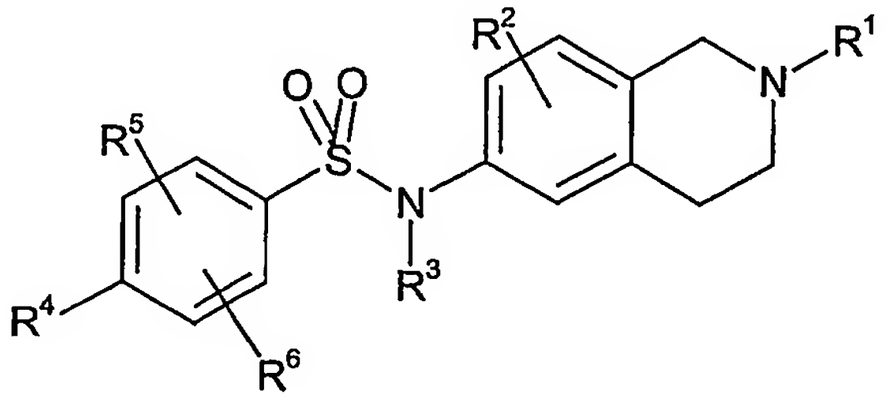
In a preferred aspect, m is 2 and n is 1 and the invention is a compound of formula (IC):



(IC)

or a pharmaceutically acceptable salt or solvate thereof wherein groups R^1 to R^6 have any of the meanings as given hereinbefore.

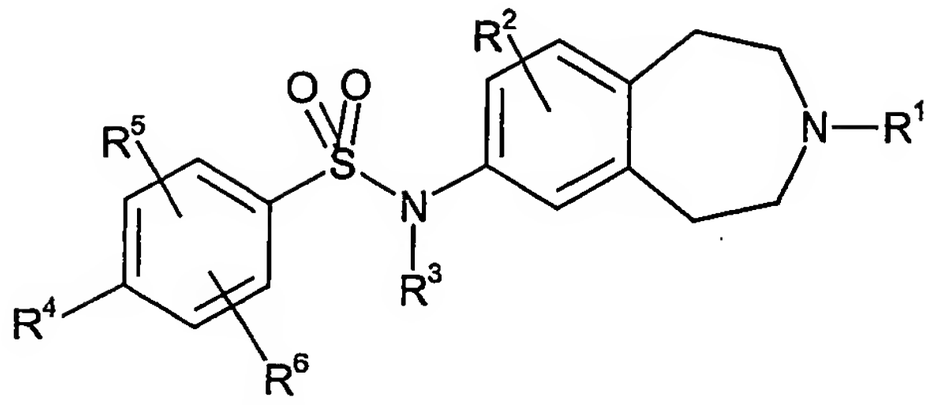
In a preferred aspect, m is 1 and n is 2 and the invention is a compound of formula (ID):



(ID)

or a pharmaceutically acceptable salt or solvate thereof wherein groups R^1 to R^6 have any of the meanings as given hereinbefore.

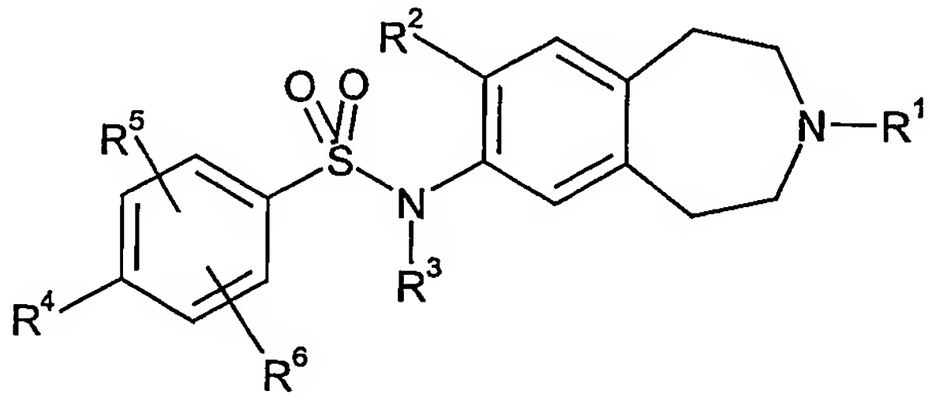
In a preferred aspect, m is 2 and n is 2 and the invention is a compound of formula (IE):



(IE)

or a pharmaceutically acceptable salt or solvate thereof wherein groups R^1 to R^6 have any of the meanings as given hereinbefore.

In a preferred aspect, m is 2 and n is 2 and R^2 is located at the para-position relative to the group B i.e. the invention is a compound of formula (IF):



(IF)

or a pharmaceutically acceptable salt or solvate thereof wherein groups R^1 to R^6 have any of the meanings as given hereinbefore.

According to a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IA) or a pharmaceutically acceptable salt or solvate thereof wherein the groups A, B and R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IB) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IC) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (ID) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IE) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

According to a further aspect of the invention, there is provided a compound of formula (IF) or a pharmaceutically acceptable salt or solvate thereof wherein the groups R^1 to R^6 have any of the meanings as given hereinbefore and Z represents oxygen or C_{1-6} alkylene.

In a preferred aspect, compounds of formula (I) are of the formula (IB), (IC), (IE) and (IF) or a pharmaceutically acceptable salt or solvate thereof wherein groups R^1 to R^6 have any of the meanings as given hereinbefore.

Particular compounds according to the invention include those incorporated in Tables 1 to 3 and those specifically exemplified and named hereinafter including, without limitation:-

4-Butyl-N-(2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide;

4-Butyl-N-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide;

4-Butyl-N-methyl-N-(2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;

4-Butyl-N-methyl-N-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;

4-Butyl-N-(8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;

4-Butyl-N-(3-methyl-8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;

4-Butyl-N-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzenesulfonamide;

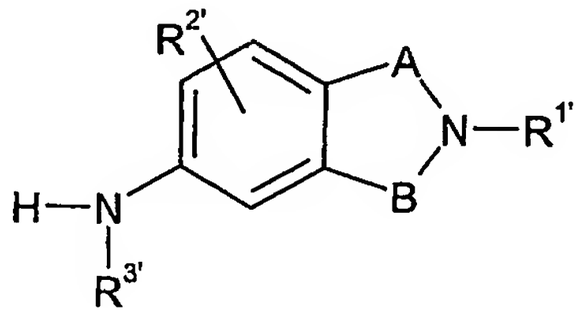
4-Butyl-N-(2,3-dihydro-1H-isoindol-5-yl)-benzenesulfonamide hydrochloride; and

4-Butyl-N-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-benzenesulfonamide.

The compounds of the present invention may be in the form of their free base or physiologically acceptable salts thereof, particularly the monohydrochloride or monomesylate salts.

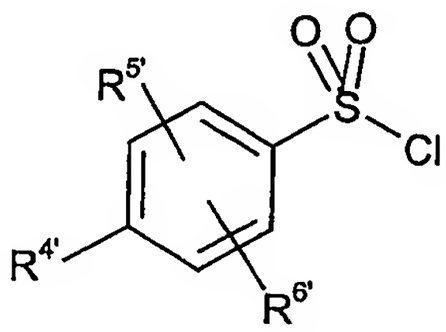
The present invention also provides a general process (A) for preparing compounds of formula (I) which process comprises:

reacting a compound of formula (II)



(II)

with a compound of formula (III)



(III)

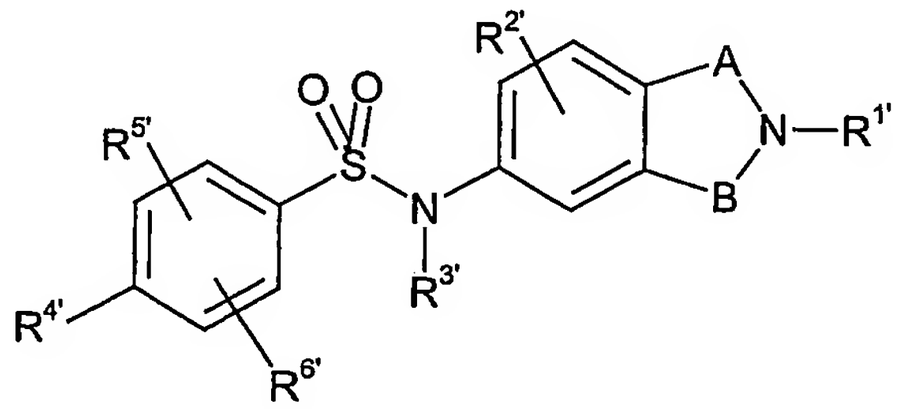
wherein $R^{1'}$-$R^{6'}$ represent R^1 to R^6 as hereinbefore defined, or are groups that may be readily convertible to R^1 to R^6. For example, conversion of an $R^{4'}$ bromo substituent to an R^4 alkyl

group can be achieved by Kumada coupling i.e. treatment of the bromo compound with an alkyl Grignard reagent in the presence of a palladium catalyst.

This general method (A) can be conveniently performed by mixing the two components in a suitable solvent such as pyridine or dichloromethane (in the presence of a base), at 0°C.

The present invention also provides a general process (B) for preparing compounds of formula (I) which process comprises:

converting a compound of formula (I)



(I)

wherein the substituents $R^{1'}$ to $R^{5'}$ are the same as in formula (I) or convertible into another compound of formula (I) (using conventional techniques).

Interconversion of one of the $R^{1'}$ to $R^{5'}$ groups to the corresponding R^1 to R^5 group typically arises when one compound of formula (I) is used as the immediate precursor of another compound of formula (I), or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

For example, conversion of $R^{1'}$ from a BOC group to hydrogen is conducted by the treatment of the N-BOC protected compound with hydrogen chloride in ethanol or dioxan at room temperature.

Conversion of $R^{1'}$ from hydrogen to an alkyl group is conducted by the treatment of the NH compound with the appropriate aldehyde in dichloroethane in the presence of a reducing agent, such as sodium triacetoxyborohydride, or by the treatment of the NH compound with the appropriate alkyl halide, such as iodomethane, under standard alkylation conditions (potassium carbonate in DMF at 60°C).

Conversion of $R^{3'}$ from hydrogen to an alkyl group is conducted by the treatment of the sulfonamide NH compound with the appropriate alcohol, such as methanol, under Mitsunobu conditions i.e. treatment with diisopropyl azodicarboxylate/triphenylphosphine and methanol in tetrahydrofuran at room temperature.

Compounds of formula (II) are known in the literature or can be prepared by known processes, for example the reduction of the corresponding nitro compound by catalytic hydrogenation as described in WO99/14197. Suitable examples of an $R^{1'}$ protecting group are trifluoroacetyl or the t-butoxycarbonyl (BOC) group.

Compounds of formula (III) are commercially available or may be prepared by established procedures, for example chlorosulfonylation of a suitable substituted aromatic precursor, using chlorosulfonic acid, for example as described in Bull. Soc. Chim. France, 1964, (2), 248-250.

Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular the D_3 and D_2 receptors, and are useful in the treatment of disease states which

require modulation of such receptors, such as psychotic conditions. Many of the compounds of formula (I) have also been found to have greater affinity for dopamine D_3 than for D_2 receptors. The therapeutic effect of many antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D_2 receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the dopamine D_3 receptor may give rise to beneficial antipsychotic activity without significant eps. (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No. 4, 295-314, 1993). Additionally, certain compounds of formula (I) have antagonist affinity for the serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 receptors. These additional properties may give rise to enhanced anti-psychotic activity (e.g. improved effects on cognitive dysfunction) and/or reduced eps. These could include, but are not limited to, attenuation of cognitive symptoms via 5-HT_6 receptor blockade (see Reavill, C. and Rogers, D.C., 2001, Investigational Drugs 2, 104-109), and reduced anxiety (see for example Kennett et al., Neuropharmacology 1997 Apr-May; 36 (4-5): 609-20), protection against EPS (Reavill et al., Brit. J. Pharmacol., 1999; 126: 572-574) and antidepressant activity (Bristow et al., Neuropharmacology 39:2000; 1222-1236) via 5-HT_{2C} receptor blockade.

Compounds of formula (I) may also exhibit affinity for other receptors not mentioned above, resulting in beneficial antipyschotic activity.

The compounds of formula (I) are of use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders. Furthermore, they may have utility as adjunct therapy in Parkinsons Disease, particularly with compounds such as L-DOPA and possibly dopaminergic agonists, to reduce the side effects experienced with these treatments on long term use (e.g. see Schwartz et al., Brain Res. Reviews, 1998, 26, 236-242). From the localisation of D_3 receptors, it could also be envisaged that the compounds could also have utility for the treatment of substance abuse where it has been suggested that D3 receptors are involved (e.g. see Levant, 1997, Pharmacol. Rev., 49, 231-252). Examples of such substance abuse include alcohol, cocaine, heroin and nicotine abuse. Other conditions which may be treated by the compounds include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety; agitation; tension; social or emotional withdrawal in psychotic patients; cognitive impairment including memory disorders such as Alzheimer's disease; psychotic states associated with neurodegenerative disorders, e.g. Alzheimer's disease; eating disorders; obesity; sexual dysfunction; sleep disorders; emesis; movement disorders; obsessive-compulsive disorders; amnesia; aggression; autism; vertigo; dementia; circadian rhythm disorders; and gastric motility disorders e.g. IBS.

Therefore, the invention provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in a condition which requires modulation of a dopamine receptor.

The invention also provides a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

The invention also provides the use of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

The invention also provides a method of treating a condition which requires modulation of a dopamine receptor, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect, the invention provides a method of treating psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as hereinbefore described or a pharmaceutically acceptable salt or solvate thereof.

A preferred use for dopamine antagonists according to the present invention is in the treatment of psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment.

"Treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) as hereinbefore described or a pharmaceutically (i.e. physiologically) acceptable salt thereof and a pharmaceutically (i.e. physiologically) acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

The compounds of formula (I) as hereinbefore described may be administered by any convenient method, for example by oral, parenteral (e.g. intravenous), buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) as hereinbefore described and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Biological Test Methods

Binding experiments on cloned dopamine (e.g. D2 and D3) receptors

The ability of the compounds to bind selectively to human D2/D3 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [^{125}I]-Iodosulpride binding to human D2/D3 receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by centrifugation (from suspension cultures), and were washed two or three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -80°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

Preparation of CHO cell membranes: Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold Extraction buffer; 5mM EDTA, 50mM Trizma pre-set crystals (pH7.4@37°C), 1mM $MgCl_2$, 5mM KCl and 120mM NaCl. The suspension was homogenised using an Ultra-Turrax at full speed for 15 seconds. The homogenate was centrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C centrifuge. Supernatant was discarded, and homogenate re-suspended in extraction buffer then centrifugation was repeated. The final pellet was resuspended in 50mM Trizma pre-set crystals (pH 7.4 @ 37°C) and stored in 1ml aliquot tubes at –80°C (D2 = 3.0E+08 cells, D3 = 7.0E+07 cells and D4 = 1.0E+08 cells). The protein content was determined using a BCA protocol and bovine serum albumin as a standard (Smith, P. K., et al., Measurement of protein using bicinchoninic acid. Anal. Biochem. 150, 76-85 (1985)).

Binding experiments: Crude D2/D3 cell membranes were incubated with 0.03nM [^{125}I]-Iodosulpride (~2000 Ci/mmol; Amersham, U. K., and the test compound in a buffer containing 50mM Trizma pre-set crystals (pH 7.4 @ 37°C), 120mM NaCl, 5mM KCl, 2mM $CaCl_2$, 1mM $MgCl_2$, 0.3% (w/v) bovine serum albumin. The total volume is 0.2ml and incubated in a water bath at 37°C for 40 minutes. Following incubation, samples were filtered onto GF/B Unifilters using a Canberra Packard Filtermate, and washed four times with ice-cold 50mM Trizma pre-set crystals (pH 7.4 @ 37°C). The radioactivity on the filters was measured using a Canberra Packard Topcount Scintillation counter. Non-specific binding was defined with 10μM SKF-102161 (YM-09151). For competition curves, 10 serial log concentrations of competing cold drug were used (Dilution range: 10μM-10pM).

Competition curves were analysed using Inflexion, an iterative curve fitting programme in Excel. Results were expressed as pK_i values where
$pK_i = -\log10[Ki]$.

The exemplified compounds have pK_i values within the range of 7.1 – 9.4 at the dopamine D_3 receptor.
The exemplified compounds have pK_i values within the range of 6.0 – 8.8 at the dopamine D_2 receptor.

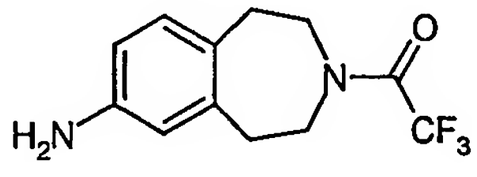
Binding experiments on cloned 5-HT_6 receptors
Compounds can be tested following the procedures outlined in WO 98/27081.
The exemplified compounds have pK_i values within the range of 6.4 – 9.0 at the serotonin 5-HT_6 receptor.

Binding experiments on cloned 5-HT_{2A} and 5-HT_{2C} receptors
Compounds can be tested following the procedures outlined in WO 94/04533.
The exemplified compounds have pK_i values within the range of 6.3 – 9.2 at the serotonin 5-HT_{2A} and 5-HT_{2C} receptors.

The invention is further illustrated by the following non-limiting examples:

Description 1

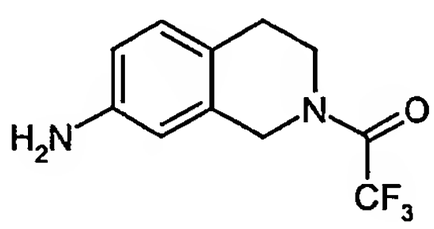
1-(7-Amino-1,2,4,5-tetrahydro-3-benzazepin-3-yl)-2,2,2-trifluoro-ethanone (D1)



The title compound was prepared from 7-nitro-1,2,4,5-tetrahydro-3-benzazepine by reaction with trifluoroacetic anhydride followed by hydrogenation, using a procedure similar to that described in WO 9914197. MH^+ 259

Description 2

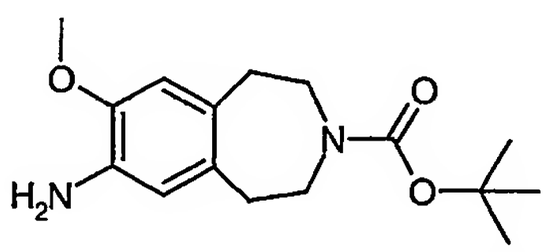
1-(7-Amino-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone (D2)



The title compound was prepared using a similar methodology to that described in WO 9914197. MH^+ 245

Description 3

7-Amino-8-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester (D3)



a) 7-Methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester

To a solution of 7-hydroxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester (5g, 19mmol) in dimethylformamide (50mL) was added potassium carbonate (3.4g, 25mmol) and methyl iodide (3.25mL, 60mmol). The mixture was heated to 30°C for 12h. The solvent was evaporated and the residue partitioned between dichloromethane (100mL) and water (100mL). The organic layer was separated and evaporated to give the crude product as a colourless oil (5.3g, 100%).

b) 7-Methoxy-8-nitro-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester

To a mixture of 7-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester (5.3g, 19mmol) in glacial acetic acid (100mL) and acetic anhydride (10mL) at 0°C was added a mixture of nitric acid (70% aqueous, 5g, 55mmol) dropwise in glacial acetic acid

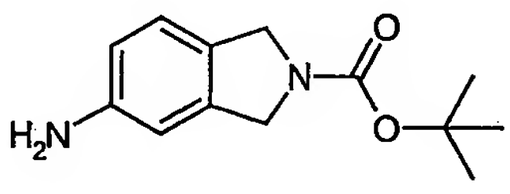
(100mL) and acetic anhydride (10mL) maintaining the temperature below 5°C. The mixture was stirred at room temperature for 2h and then poured into ice/water (500ml). The aqueous was extracted with dichloromethane (2 x 200mL) and the combined organic portions were neutralised with saturated sodium bicarbonate solution. The dichloromethane layer was evaporated and the residue chromatographed on silica gel (eluent: hexane/dichloromethane (1:1) to dichloromethane) to give the product as a colourless solid (1.5g, 25%).

c) 7-Amino-8-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester

To a solution of 7-methoxy-8-nitro-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert-butyl ester (1.5g, 4.7mmol) in ethanol (80mL) was added palladium on charcoal (10%, 0.5g). The mixture was stirred under an atmosphere of hydrogen for 2h and then filtered. The solvent was evaporated to give the title compound as a colourless solid (1.35g, 100%).
Mass spectrum AP^+: Found 193 ($[M\text{-}Boc]^+$). $C_{16}H_{24}N_2O_3$ requires 292. 1H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.76 (4H, m), 3.51 (4H, m), 3.65 (2H, s), 3.82 (3H, s), 6.50 (1H, m), 6.56 (1H, m).

Description 4

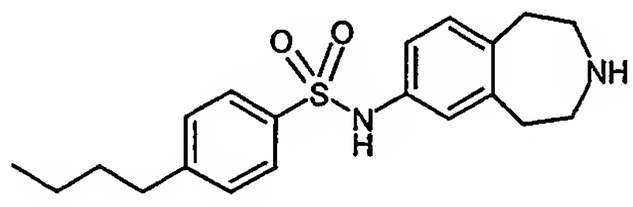
5-Amino-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester (D4)



The title compound was prepared from 5-nitro-isoindoline by reaction with di-t-butyl dicarbonate followed by hydrogenation, using a similar procedure to that described in WO 9914197. ^1H NMR: δ $CDCl_3$ 1.52 (9H, s), 4.74 (2H, s), 4.77 (2H, s), 7.4 (1H, m), 8.2 (2H, m).

Example 1

4-Butyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E1)



a) 4-Butyl-*N*-[3-(2,2,2-trifluoro-ethanoyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]-benzenesulfonamide

The amine D1 (0.5 g, 1.9 mmol) was dissolved in pyridine (8 mL) and cooled to 0°C. To this stirred solution was added dropwise a solution of 4-n-butylphenylsulfonyl chloride (0.89 g; 3.8 mmol), and the resultant mixture stirred at room temperature for 18 h. The reaction mixture was then poured onto brine and extracted with dichloromethane. The combined organic layers were washed with citric acid solution followed by brine, then dried and

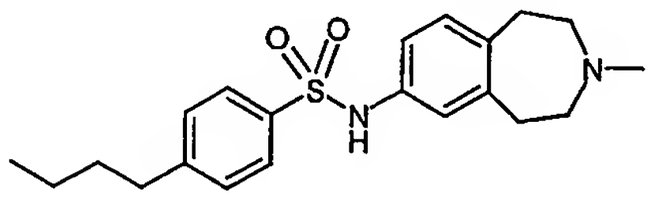
evaporated. Chromatography of the crude product on silica eluting with 30% ethyl acetate/hexane afforded the product (0.7 g) MH^+ 398.

b) 4-Butyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide

The product from a) was dissolved in 2M ammonia in methanol (30 mL) and water (6 mL) added to the stirred solution. Stirring was continued for 18 h, then the solution evaporated to dryness. Application of the crude product to an SCX ion exchange cartridge, followed by elution with methanol followed by 1% ammonia in methanol afforded the title compound (0.44 g). MH^+ 359. ^1H NMR: δ $CDCl_3$ 0.91 (3H, t), 1.29 (2H, m), 1.57 (2H, m), 2.63 (2H, t), 2.82 (4H, m), 2.90 (4H, m), 6.78 (2H, m), 6.94 (1H, d), 7.25 (2H, d), 7.65 (2H, d).

Example 2

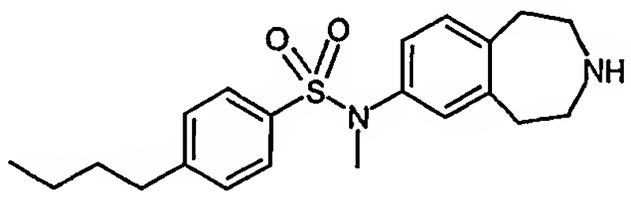
4-Butyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide (E2)



A solution of E1 (140 mg) in dichloroethane (20 mL) was treated with formalin (0.3 mL) followed by sodium triacetoxyborohydride (350 mg). The mixture was stirred for 18 h, then added to sodium bicarbonate solution and extracted with dichloromethane. The combined organic extracts were washed with brine, dried and evaporated to afford the crude product. Chromatography on silica, eluting with 2% methanol in dichloromethane containing 0.5% aqueous ammonia, afforded the title compound (47 mg). MH^+ 373. ^1H NMR: δ $CDCl_3$ 0.91 (3H, t), 1.32 (2H, m), 1.57 (2H, m), 2.34 (3H, s), 2.50 (4H, m), 2.63 (2H, t), 2.83 (4H, m), 6.76 (2H, m), 6.94 (1H, d), 7.24 (2H, d), 7.64 (2H, d).

Example 3

4-Butyl-*N*-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E3)



a) 4-Butyl-*N*-methyl-*N*-[3-(2,2,2-trifluoro-ethanoyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]-benzenesulfonamide

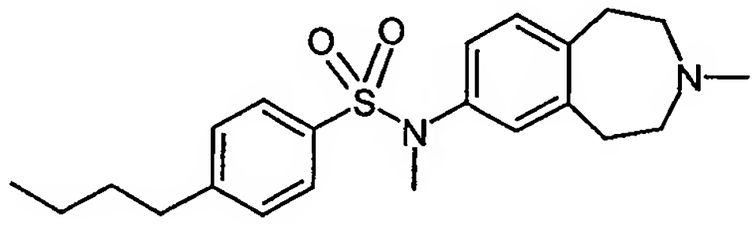
The trifluoroacetamide E1a (205 mg) was dissolved in dry tetrahydrofuran (7 mL) containing triphenylphosphine (150 mg) and dry methanol (150 mg). To this stirred solution was added di-isopropylazodicarboxylate (113 mg) and the mixture stirred at room temperature for 18 h. The solvent was then evaporated and the residue chromatographed on silica using 12% ethyl acetate/hexane as eluant to afford the product (200 mg). MH^+ 468.

b) 4-Butyl-*N*-methyl-*N*-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride

Deprotection of the product from a) using a procedure similar to that in E1b afforded the title compound (180 mg), which was isolated as the hydrochloride salt. MH^+ 373. ^1H NMR: δ $CDCl_3$ (free base) 0.93 (3H, t), 1.35 (2H, m), 1.62 (2H, m), 2.67 (2H, t), 2.88 (8H, m), 3.13 (3H, s), 6.76 (1H, m), 6.82 (1H, s), 6.99 (1H, d), 7.23 (2H, d), 7.47 (2H, d), 8.01 (1H, s).

Example 4

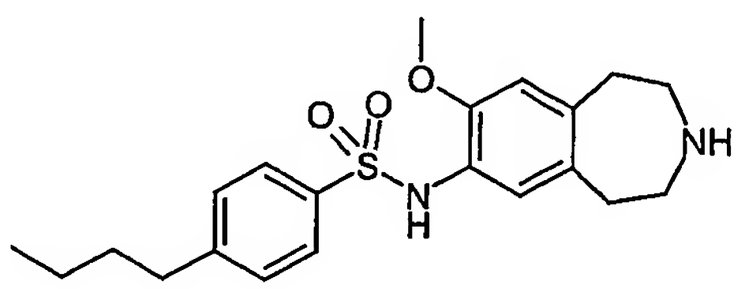
4-Butyl-*N*-methyl-*N*-(3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzene-sulfonamide hydrochloride (E4)



The title compound was prepared from Example 3 using a procedure similar to that for Example 2, and the product isolated as the hydrochloride salt. MH^+ 387. ^1H NMR: δ $CDCl_3$ 0.93 (3H, t), 1.36 (2H, m), 1.60 (2H, m), 2.37 (3H, s), 2.56 (4H, b s), 2.67 (2H, t), 2.86 (4H, b s), 3.13 (3H, s), 6.78 (1H, m), 6.83 (1H, s), 6.99 (1H, d), 7.25 (2H, d), 7.46 (2H, d).

Example 5

4-Butyl-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E5)



a) 7-(4-Butyl-benzenesulfonylamino)-8-methoxy-1,2,4,5-tetrahydro-3-benzazepine-3-carboxylic acid tert butyl ester

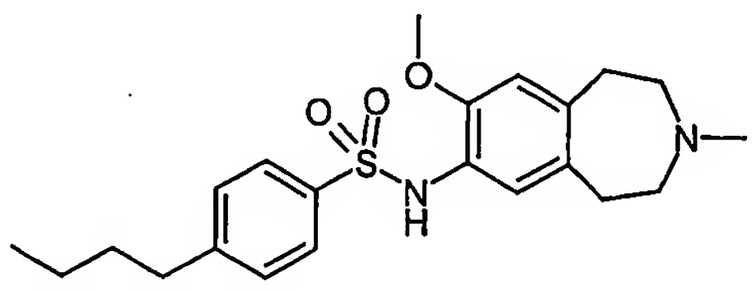
The BOC protected intermediate was prepared from D3 and 4-n-butylphenylsulfonyl chloride using a procedure analogous to that for Example 1a. MH^+ 489.

b) 4-Butyl-*N*-(8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride

The title compound was prepared from a) by treatment with a solution of ethanolic hydrogen chloride, followed by the addition of ether to precipitate the product. MH^+ 389. ^1H NMR: δ DMSO 0.88 (3H, t, J = 7.3Hz), 1.27 (2H, m), 1.52 (2H, m), 2.62 (2H, t, J = 7.6Hz), 2.99 (4H, m), 3.09 (4H, m), 3.32 (3H, s), 6.78 (1H, s), 7.04 (1H, s), 7.33 (2H, d, J = 8.3Hz), 7.59 (2H, d, J = 8.3Hz), 9.18 (3H, broad m)

Example 6

4-Butyl-*N*-(3-methyl-8-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-benzenesulfonamide hydrochloride (E6)

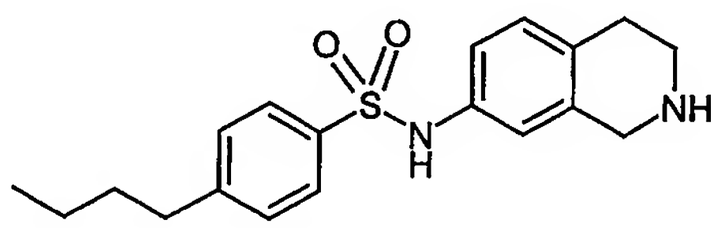


The title compound was prepared from Example 5 using a procedure similar to that for Example 2, and the product isolated as the hydrochloride salt. MH^+ 403. ^1H NMR: δ $CDCl_3$ 0.89 (3H, m), 1.23-1.38 (2H, m), 1.5-1.62 (2H, m), 2.35 (3H, s), 2.47-2.53 (4H, m), 2.58-2.64 (2H, m), 2.79-2.87 (4H, m), 3.54 (3H, s), 6.46 (1H, s), 6.70-6.95 (1H, br, s), 7.16-7.20 (2H, m), 7.25 (1H, s), 7.59-7.65 (2H, m).

Examples 10-76 and 82 were prepared using analogous procedures to Examples 1-6 using the appropriate starting materials, with the products being isolated as either the free bases or hydrochloride salts. All ^1H NMR are consistent with the structures shown.

Example 7

4-Butyl-*N*-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzenesulfonamide (E7)

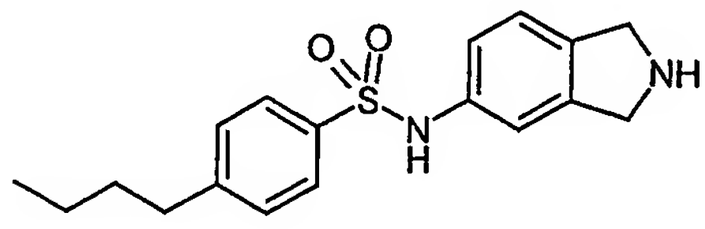


The title compound was prepared from the aniline D2 and 4-n-butylphenylsulfonyl chloride using a procedure similar to Example 1. MH^+ 345. ^1H NMR: δ $CDCl_3$ 0.91 (3H, t), 1.33 (2H, m), 1.57 (2H, m), 2.63 (2H, t), 2.71 (2H, t), 3.08 (2H, t), 3.89 (2H, s), 6.72 (1H, s), 6.79 (1H, m), 6.93 (1H, d), 7.23 (2H, d), 7.63 (2H, d).

Examples 38-54 and 77-81 were prepared using analogous procedures to Examples 1-7 using the appropriate starting materials, with the products being isolated as either the free bases or hydrochloride salts. All ^1H NMR are consistent with the structures shown.

Example 8

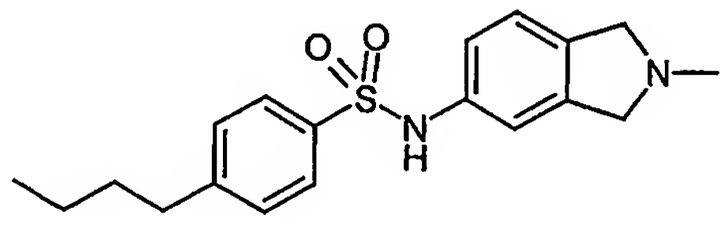
4-Butyl-*N*-(2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide hydrochloride (E8)



The title compound was prepared from D4 and 4-n-butylphenylsulfonyl chloride using a procedure to that for Examples 1a and 5b. MH^+ 331. ^1H NMR: δ DMSO 0.87 (3H, m), 1.2 (2H, m), 1.5 (2H, m), 2.62 (2H, m), 4.4 (4H, m), 7.07 (1H, d), 7.16 (1H, s), 7.24 (2H, d), 7.35 (2H, m), 7.68 (2H, d), 9.8 (2H, m), 10.46 (1H, m).

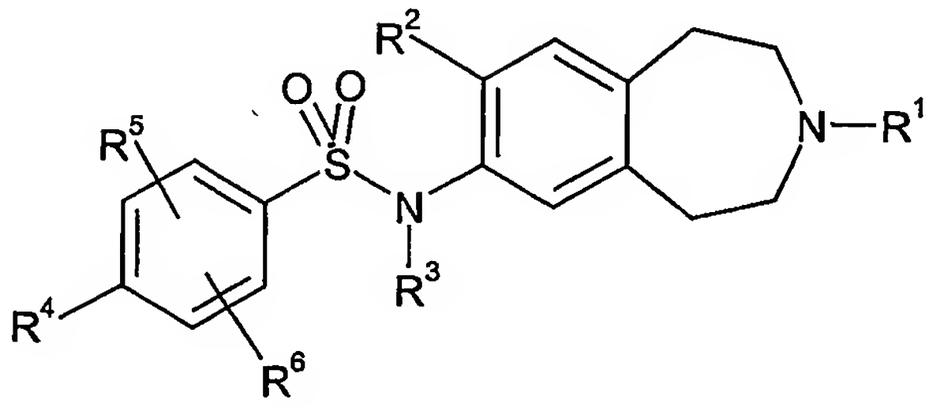
Example 9

4-Butyl-*N*-(2-methyl-2,3-dihydro-1*H*-isoindol-5-yl)-benzenesulfonamide (E9)



The title compound was prepared from E8 using a procedure similar to that for E2. MH^+ 345. ^1H NMR: δ DMSO 0.86 (3H, m), 1.24 (2H, m), 1.54 (2H, m), 2.49 (2H,s), 2.61 (2H, m), 3.68 (4H, s), 6.88 (1H, d), 6.93 (1H, s), 7.05 (H, d), 7.35 (2H, d), 7.64 (2H, d), 10.1 (1H, m).

All of the compounds listed below in Table 1 relate to compounds of formula (IF):



(IF)

Table 1

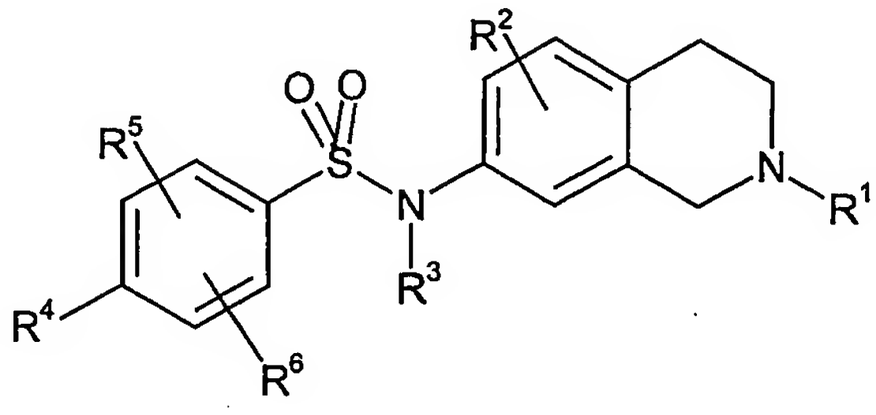
Example	R^1	R^2	R^3	R^4	R^5	R^6	MH^+
1	H	H	H	n-butyl	H	H	359
2	Me	H	H	n-butyl	H	H	373
3	H	H	Me	n-butyl	H	H	373
4	Me	H	Me	n-butyl	H	H	387
5	H	OMe	H	n-butyl	H	H	389
6	Me	OMe	H	n-butyl	H	H	403
10	H	H	H	n-propyl	H	H	345
11	Me	H	H	n-propyl	H	H	359
12	H	H	H	i-propyl	H	H	345
13	Me	H	H	i-propyl	H	H	359
14	H	H	H	1,1-diMepropyl	H	H	373
15	Me	H	H	1,1-diMepropyl	H	H	387
16	Me	H	H	t-butyl	H	H	373
17	H	H	H	n-pentyl	H	H	373
18	Me	H	H	n-pentyl	H	H	387
19	Me	H	H	cyclohexyl	H	H	399
20	Me	H	H	I	H	H	443
21	Me	H	H	CF_3	H	H	385
22	Me	H	H	OCF_3	H	H	401
23	H	H	H	O-propyl	H	H	361
24	Me	H	H	O-propyl	H	H	375
25	H	H	H	O-butyl	H	H	375
26	Me	H	H	O-butyl	H	H	389
27	Et	H	H	n-butyl	H	H	387
28	n-Pr	H	H	n-butyl	H	H	401
29	i-Pr	H	H	n-butyl	H	H	401
30	H	H	Et	n-butyl	H	H	387
31	Me	H	Et	n-butyl	H	H	401
32	H	H	n-Pr	n-butyl	H	H	401
33	Me	H	n-Pr	n-butyl	H	H	415

Table 1 (continued)

Example	R^1	R^2	R^3	R^4	R^5	R^6	MH^+
34	H	H	i-Pr	n-butyl	H	H	401
35	Me	H	i-Pr	n-butyl	H	H	415
36	H	Br	H	n-butyl	H	H	438
37	H	EtO	H	n-butyl	H	H	403
55	Me	EtO	H	n-butyl	H	H	417
56	H	MeO	H	n-propyl	H	H	375
57	H	MeO	H	i-propyl	H	H	375
58	H	MeO	H	1,1-diMepropyl	H	H	403
59	H	MeO	H	n-pentyl	H	H	403
60	H	MeO	H	c-hexyl	H	H	415
61	H	MeO	H	OCF_3	H	H	417
62	Me	MeO	H	OCF_3	H	H	431
63	Me	MeO	H	O-propyl	H	H	391
64	Me	MeO	H	O-butyl	H	H	405
65	H	i-PrO	H	n-butyl	H	H	417
66	Me	i-PrO	H	n-butyl	H	H	431
67	H	MeO	Me	n-butyl	H	H	403
68	Me	MeO	Me	n-butyl	H	H	417
69	H	MeO	i-Pr	n-butyl	H	H	431
70	Me	MeO	i-Pr	n-butyl	H	H	445
71	H	Et	H	n-butyl	H	H	387
72	Me	Et	H	n-butyl	H	H	401
73	Me	(2-thienyl)	H	n-butyl	H	H	455
74	H	(2-thienyl)	H	n-butyl	H	H	441
75	Me	(2-furyl)	H	n-butyl	H	H	425
76	Me	Br	H	n-butyl	H	H	452
82	Me	MeO	H	cyclohexyl	H	H	429

All of the compounds listed below in Table 2 relate to compounds of formula (IC):

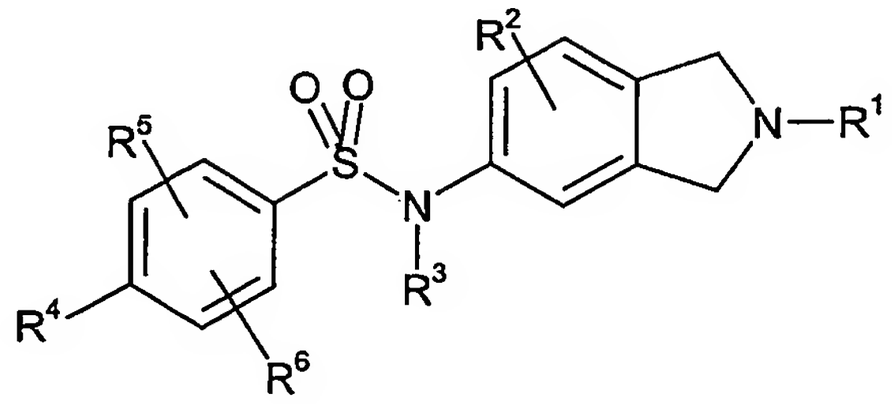
Table 2



(IC)

Example	R^1	R^2	R3	R^4	R^5	R^6	MH^+
7	H	H	H	n-butyl	H	H	345
38	Me	H	H	n-butyl	H	H	359
39	Me	H	H	n-propyl	H	H	345
40	Me	H	H	i-propyl	H	H	345
41	H	H	H	n-pentyl	H	H	359
42	Me	H	H	n-pentyl	H	H	373
43	H	H	H	cyclohexyl	H	H	371
44	Me	H	H	cyclohexyl	H	H	385
45	H	H	H	O-n-butyl	H	H	361
46	Me	H	H	O-n-butyl	H	H	375
47	Et	H	H	n-butyl	H	H	373
48	n-Pr	H	H	n-butyl	H	H	387
49	i-Pr	H	H	n-butyl	H	H	387
50	H	H	Me	n-butyl	H	H	359
51	Me	H	Me	n-butyl	H	H	373
52	H	H	Et	n-butyl	H	H	373
53	Me	H	Et	n-butyl	H	H	387
54	Me	H	i-Pr	n-butyl	H	H	401
77	H	6-MeO	H	i-propyl	H	H	361
78	H	6-MeO	H	n-butyl	H	H	375
79	H	6-MeO	H	c-hexyl	H	H	401
80	H	6-MeO	H	OCF_3	H	H	403
81	H	6-MeO	H	O-n-Pr	H	H	377

All of the compounds listed below in Table 3 relate to compounds of formula (IB):



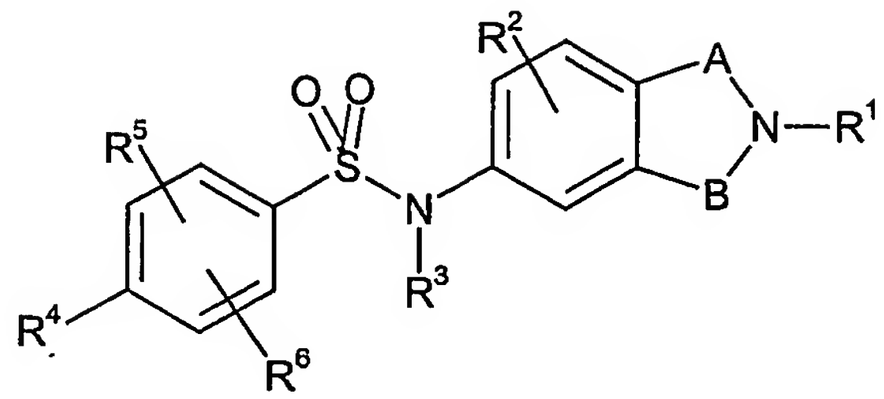
(IB)

Table 3

Example	R^1	R^2	R^3	R^4	R^5	R^6	MH^+
8	H	H	H	n-butyl	H	H	331
9	Me	H	H	n-butyl	H	H	345

Claims

1. A compound of formula (I)



(I)

wherein

A and B represent the groups $-(CH_2)_m-$ and $-(CH_2)_n-$ respectively;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pC_{3-6}$cycloalkyloxy, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^7R^8$, $-SO_2NR^7R^8$, $-(CH_2)_pNR^7R^8$, $-(CH_2)_pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl or a fused bicyclic heterocyclic ring system;

R^3 represents hydrogen or C_{1-6}alkyl;

R^4 represents halogen, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl or $-(CH_2)_pC_{3-6}$cycloalkyloxy;

R^5 and R^6 each independently represent hydrogen, halogen, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_pC_{3-6}$cycloalkyl, $-(CH_2)_pC_{3-6}$cycloalkyloxy, $-COC_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-SOC_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-CO_2C_{1-6}$alkyl, $-CO_2NR^7R^8$, $-SO_2NR^7R^8$, $-(CH_2)_pNR^7R^8$, $-(CH_2)_pNR^7COR^8$, optionally substituted aryl, optionally substituted heteroaryl or a fused bicyclic heterocyclic ring system;

R^7 and R^8 each independently represent hydrogen or C_{1-6}alkyl;

m and n independently represent an integer selected from 1 and 2;

p independently represents an integer selected from 0, 1, 2 and 3;

or a pharmaceutically acceptable salt or solvate thereof,

with the proviso that the compounds 4-methyl-N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-benzenesulfonamide, 7-(4-chlorophenyl)sulfonamido-1,2,3,4-tetrahydroisoquinoline hydrochloride and N-(2-ethyl-5-isoindolinyl)-p-toluenesulfonamide are excluded.

2. A compound of formula (I) which is

4-Butyl-N-(2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide;

4-Butyl-N-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide;

4-Butyl-N-methyl-N-(2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;

4-Butyl-N-methyl-N-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;

4-Butyl-N-(8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;

4-Butyl-N-(3-methyl-8-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine-7-yl)-benzenesulfonamide hydrochloride;
4-Butyl-N-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-benzenesulfonamide;
4-Butyl-N-(2,3-dihydro-1H-isoindol-5-yl)-benzenesulfonamide hydrochloride; and
4-Butyl-N-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-benzenesulfonamide.

3. A pharmaceutical composition comprising a compound of formula (I) as claimed in claims 1 or 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

4. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2, for use in therapy.

5. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2 for use in a condition which requires modulation of a dopamine receptor.

6. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof according to claim 5 wherein the condition is selected from psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

7. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2 in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

8. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof according to claim 7 wherein the condition is selected from psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

9. A method of treating a condition which requires modulation of a dopamine receptor, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in claims 1 or 2.

10. A method of treating a condition according to claim 9 wherein the condition is selected from psychotic disorders, Parkinsons disease, substance abuse, dyskinetic disorders, depression, bipolar disorder, anxiety, cognitive impairment, eating disorders, obesity, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.